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A Mild and Selective Method for the Catalytic Hydrodeoxygenation of Cyanurate Activated Phenols in Multiphasic Continuous Flow

Yuhan Zhao, Georgina King, Maria H.T. Kwan, and A. John Blacker*

Institute of Process Research and Development, School of Chemistry and School of Chemical and Process Engineering, University of Leeds, Woodhouse Lane, LS2 9JT, West Yorkshire, United Kingdom

Supporting Information

ABSTRACT: A low-energy, high-selectivity approach to the catalytic hydrodeoxygenation of phenols is reported using batch or continuous flow methods to react 3 equiv of phenol with cyanuric chloride then hydrogenolyzing the triarylcyanurate intermediate to give 3 equiv of deoxo aromatic. The use of cyanuric chloride compares favorably with existing activation methods, showing improved scalability, atom efficiency, and economics. The scope of both the activation and hydrogenolysis stages are explored using lignin-related phenols. Initial development has identified that continuous stir tank reactors (CSTRs) enable a multiphasic process for converting guaiacol to anisole and at steady state overcome the catalyst deactivation issues observed in batch, seemingly caused by the cyanurate byproduct. Green chemistry aspects and the potential for industrial adoption are discussed.

INTRODUCTION

The use of lignin-derived poly(oxoaromatics) as biorenewable replacements for petrochemical-derived phenols has so far been limited to specific applications such as the flavor, vanillin.[1,2] Part of the difficulty is breakdown of lignin; another part is the separation of complex mixtures, and a third part is the removal of functional groups such as oxygen. Regarding the latter, hydrodeoxygenation (HDO) is a process to replace aromatic oxygen with hydrogen.[3] The conversion of lignin model compounds to benzene and cyclohexane has been reported recently using mild 200−240 °C conditions;[4] however, it has often required catalytic reforming at >300 °C temperature, resulting in over-reduction with complex product mixtures and catalyst deactivation.[5] For example cobalt molybdenum sulfide on alumina catalyst at 300 °C and 50 bar has been shown to convert 84% of the guaiacol to give 34% phenol, 11% catechol, 3% anisole, 1% benzene, and the remainder saturated products.[6] The extreme conditions are required because the aromatic C−O bond is strong with a length of 1.37 Å and bond energy of 460 kJ mol^{-1}, compared to the aliphatic C−O bond of 1.43 Å and 358 kJ mol^{-1}.[7] In the organic laboratory the hydrogenolysis of phenolic compounds is usually carried out by activation with trifluoromethanesulfonyl chloride followed by reduction; however, the cost of making triflates and the associated waste make this method too expensive and wasteful to consider for bulk production.[8] Reports of aryl−alkyl ether reduction, using either nickel catalysts and silane reductants, or better from an industrial perspective, a combination of metal triflate and palladium catalysts with hydrogen, both illustrate the difficulties in this transformation.[9] Another reported phenol activation method is reacting *N*-phenyl tetrazolium chloride with the phenol to make the corresponding 5-aryloxy-1-phenyltetrazoyl ethers, with similar disadvantages and low atom efficiency.[10] The electron-withdrawing and resonance stabilizing tetrazolyl group can weaken the aromatic C−O bond, facilitating its cleavage by catalytic hydrogenolysis. Alves has used X-ray crystal structures to show lengthening of the aromatic C−O bond to 1.42 Å, with the bond energy reduced by around 100 kJ mol^{-1}.[11] A better industrial reagent is cyanuric chloride, made from cyanogen chloride. It is used widely in the manufacture of fiber-reactive dyes and agrochemicals and is produced at >100 ktpa at about £1.50/kg.[12] Furthermore, it has the benefit of three electrophilic centers, with only one-third of a mole equivalent required in the S_NAr reaction with phenolate, Scheme 1.

Allan et al. have reported its reaction with a variety of phenols to produce the 1,3,5-triaryloxy-2,4,6-triazines in moderate-to-good yields,[13] though characterization of the compounds was limited to the melting point and CHN analysis, while Sagar et al. increased the yields using a microwave synthesis.[14] Forbes made triarylcyanurates with phenols, then used these in cross-linking reactions of lignosulfonate.[15] Van Muijlwijk et al. showed that, as with the tetrazole, the tricyanurate esters are also able to activate the aromatic C−O bond toward cleavage under catalytic hydrogenolysis, though no lignin-related phenols were studied.[16] A more recent study by Iranpoor has used homogeneous dichloronickel-bis-tricyclohexyl phosphine catalysts with super-stoichiometric zinc and potassium iodide to effect the same hydrogenolysis.[17] We reasoned that the use of tricyanurate esters for deoxygenation of guaiacol, vanillin, and related phenols might have industrial potential.

RESULTS AND DISCUSSION

We herein report scoping studies and development of continuous flow aryloxylation and hydrodeoxygenation of lignin-related phenols. Initially phenol activation and hydrogenolysis of sulfonated phenols occur, as shown in Scheme 2.

While the activation of both guaiacol and vanillin with triflic anhydride followed by hydrogenolysis was successful, the overall yields were low, despite a long reaction time (Entries 1 and 2), which is similar to previous observations.[8] Aryl

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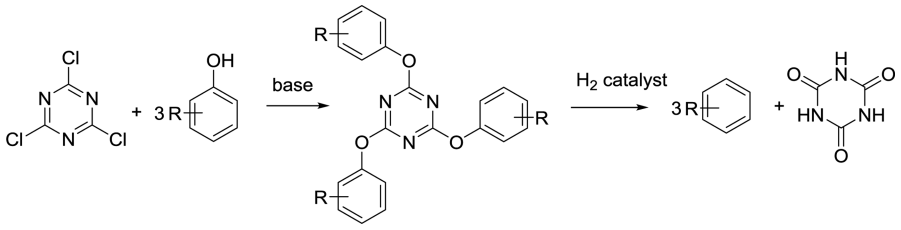
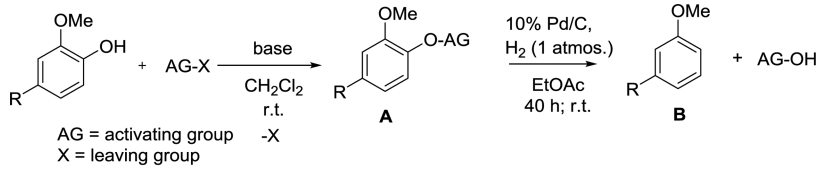
Scheme 1. Hydrodeoxygenation of Phenolic Compounds by Activation with Cyanuric Chloride and Catalytic Hydrogenolysis



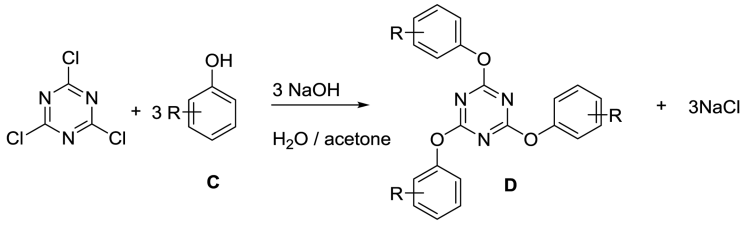
Scheme 2. Reactions of Guaiacol and Vanillin with Phenol Activation Reagents and Catalytic Hydrogenolysis



			% yield		product name
Entry	R	AG-X	**A**	**B**	**B**
1	H	Tf-OTf[f]	95	33	anisole
2	CHO	Tf-OTf[f]	60	42[a]	*m*-methyl anisole
3	H	Ms-Cl[g]	97	0[b]	anisole
4	CHO	Ms-Cl	62	0[c]	*m*-methyl anisole
5	H	*p*Ts-Cl[h]	81	0[b]	anisole
6	CHO	*p*Ts-Cl	71	0[d]	*m*-methyl anisole
7	H	Tz-Cl[i]	75	39[e]	anisole

[a]30% *m*-methoxy benzyl alcohol coproduct formed. [b]Recovered starting material. [c]*p*-(Hydroxymethyl)-2-methoxyphenyl methanesulfonate isolated in 81% yield. [d]*p*-Methyl-2-methoxyphenyl-*p*-toluenesulfonate isolated in 53%. [e]Compared to 60% published yield.[10] [f]Tf-OTf = trifluoromethanesulfonic anhydride. [g]Ms-Cl = methansulfonyl chloride. [h]pTs-Cl = *p*-toluenesulfonyl chloride. [i]Tz-Cl = 5-chloro-1-phenyl-1*H*-tetrazole.

Scheme 3. Reaction of Cyanuric Chloride with Different Phenols to Produce 1,3,5-Triaryloxy-2,4,6-triazines[a]



		product number	yield (%)[a,b]
Entry	R	**D**	**D**
1	H	**1**	89
2	2-OMe	**2**	94
3	3-OMe	**3**	92
4	4-OMe	**4**	92
5	4-CHO	**5**	85
6	2-OMe, 4-CHO	**6**	62
7	2-CO_2Me	**7**	22[c]
8	2-OMe, 4-CO_2Me	**8**	10[c]
9	2-CO_2H	**9**	76
10	2-OMe, 4-CO_2H	**10**	71

[a]Isolated mass yields, with product identities and purity confirmed by GC; see SI. [b]Run in water−acetone 1:1, 3 h at ambient temperature. [c]Run in THF with diisopropylethylamine instead of NaOH.

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mesylates and tosylates are inactive in oxidative addition and Grignard reactions, and the hydrogenolysis of guaiacyl or vanillin mesylate or tosylate compounds was also unsuccessful, the only reaction being the reduction of the formyl group to give the benzyl alcohol and tolyl derivatives (Entries 3−6). The activation of guaiacol with 5-chloro-1-phenyl-1*H*-tetrazole and its hydrogenolysis was reconfirmed (Entry 7).[10] However, the modest yield, atom inefficiency, and cost of this reagent make it unsuitable for industry use, as too with the aforementioned activating reagents. Attention was therefore turned to preparing 1,3,5-triaryloxy-2,4,6-triazines from cyanuric chloride and in situ generated sodium phenolates, shown in Scheme 3.

The reaction proceeds at ambient temperature in water/acetone with 3 equiv of phenol, during which the products precipitate, are separated by filtration and can be recrystallized from methanol. The isolated product yields are satisfactory except Entries 7 and 8, methyl salicylate and methyl vanillate that are insoluble in water and were run in THF with soluble organic base DIPEA. No evidence of the intermediate mono- or di- addition products was observed; however, these were seen and isolated as mixtures when fewer equivalents of phenol/base were used: 1 equiv of sodium guaiacolate gave a ratio of 2:12:3 mono−di−trisubstituted triazine, and 2 equiv gave a 0:1:1 ratio. This indicates that each aryl oxide addition activates the product for the next reaction and may indicate a change from S_NAr to a concerted mechanism as proposed by Williams et al.[18] Increasing the base had no benefit, other than for Entries 9 and 10 to neutralize the carboxylic acids. To improve efficiency and productivity, the reaction was evaluated in continuous flow. Since solids are formed during the reaction a plug-flow reactor was considered inappropriate; instead a newly developed lab-scale four-stage continuous stirred tank reactor (CSTR) (being reported separately) of 8 mL total volume was used; see SI. An acetone solution of cyanuric chloride was pumped simultaneously with a thrice-concentrated aqueous solution of sodium guaiacolate at combined flow rate of 0.26 mL/min and residence time (T_{res}) of 30 min; no blockages were observed during the 150 min operation. 16% conversion of **2** was realized at steady state after 90 min, and 8 mL fractions or reactor volumes (RV) were collected for a further 60 min, shown in Figure 1.

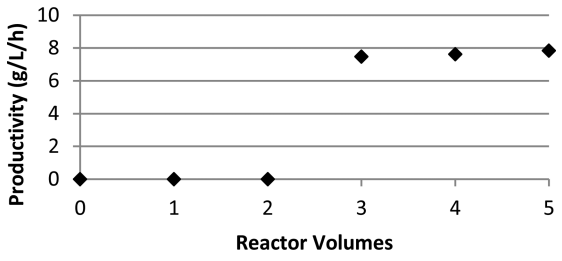

Figure 1. Continuous reaction of sodium guaiacolate with cyanuric chloride using lab-scale four-stage cascade CSTR.

The productivity achieved was 8 g/L/h which compares to 10 g/L/h achieved in batch. A higher conversion might be achieved by heating and work on this is ongoing. The identity of the product **2**, was confirmed by single-crystal X-ray analysis Figure 2.

Interestingly the bond lengths across the diarylether are significantly different: 1.453 Å aryl to oxygen and 1.361 Å triazole to the same oxygen atom. The longer bond is the one to be hydrogenolyzed. Having prepared a range of 1,3,5-triaryloxy-2,4,6-triazines at the tens of grams scale, several hydrodeoxygenation catalysts were evaluated using combinations of water and solvent to ensure solubility of **2**. A screen of Pd/C, Pt/C, Ru/C, and Raney Ni catalysts under hydrogen transfer conditions with aqueous hydrazine, triethylamine/formic acid, sodium phosphinate, or isopropanol failed to show any conversion of **2**; however, direct hydrogenation was more successful. The most promising catalyst was Johnson-Matthey 87L 10% Pd/C, used at 5% (w/w) vs substrate, TOF = 0.58 min^{-1}, giving 58% yield of anisole isolated by fractional distillation. Batch reactions were run with triazines **1**−**10**, initially at ambient temperature and hydrogen pressure, with sampling and NMR analysis confirming full conversion of starting materials in 24 h, as in Scheme 4.

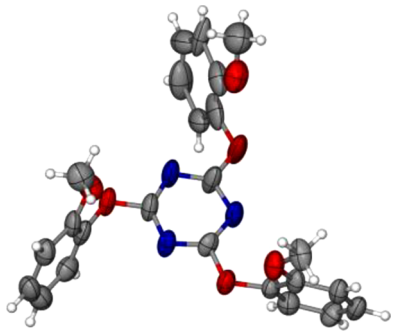

Figure 2. X-ray crystal structure of 1,3,5-triazolinyl-2,4,6-triguaiacolate, **2**.

While the conversion of **1** was high, the yield of benzene was low, though this may reflect difficulty in isolation due to evaporation during workup, shown in Entry 1. On the other hand, the yield of anisole from any of the regioisomers **2**, **3**, or **4** was good, shown in Entries 2−4. The overall conversion of guaiacol to anisole was 81% over both the activation and the hydrogenolysis steps. Aldehyde **5** from 4-hydroxy benzaldehyde and **6** from vanillin were reduced under these conditions to produce benzyl alcohol and 3-methylanisole (via the corresponding benzyl alcohol, Entries 5 and 6), while the triazine from methyl vanillate produced methyl 3-methoxybenzoate (Entry 8). Monitoring the rate of hydrogen uptake with **2** under the same conditions showed a maximum productivity of 4.5 g/L/h after 1 h that slowed over 5 h. An examination of the catalyst at the end of reaction showed a gray surface coating that may be linked to the low recovery of cyanuric acid byproduct. Washing the catalyst with water enabled the isolation of small amounts of cyanuric acid, as determined by comparison of the IR spectrum to an authentic standard; see the SI. A control reaction in which cyanuric acid was exposed to the same catalyst and conditions provided recovery of only half the mass. Moreover, higher hydrogen pressures resulted in lower cyanuric acid recovery. These results indicate both catalyst surface poisoning and cyanuric acid decomposition, possibly to isocyanate or the corresponding acid. The addition of triethylamine had no effect on the reaction rate; however, the physical appearance of the catalyst was significantly different with change in median particle size from 20 μm, to two maxima at 4 and 50 μm.[19] Energy dispersive X-ray (EDX) spectroscopy showed that once-used catalyst had a higher Pd:C ratio of 53:5, compared with fresh, 79:11, or a reaction cofed with triethylamine, 73:11. The study of the kinetics of the hydrogenolysis of **2** showed the order of reaction to be 0.9, probably less than unity because of the catalyst deactivation.

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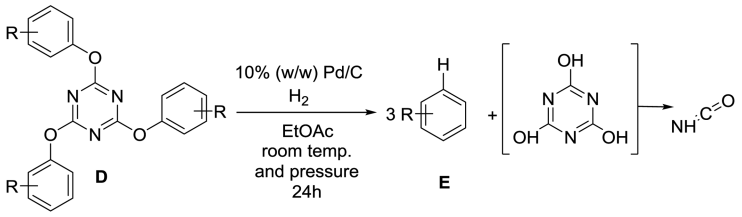
Scheme 4. Isolated Yields of Aromatics E, at Complete Conversion of D[a]



Entry	product number D	product name E	yield (%)[a,b] E
1	**1**	benzene	10
2	**2**	anisole	86
3	**3**	anisole	68
4	**4**	anisole	68
5	**5**	benzyl alcohol	30
6	**6**	3-methylanisole	14
7	**7**	methyl benzoate	10
8	**8**	methyl 3-methoxybenzoate	12
9	**9**	benzoic acid	21
10	**10**	3-methoxybenzoic acid	58

[a]Isolated mass yields, with product identities and purity confirmed by GC; see SI. [b]No byproducts or impurities were identified in the crude isolate.

The reaction rate constant k_{obs} was determined to be 0.012 min^{-1}. An aspect of this study was to develop methods that have potential for industrial exploitation; therefore, a continuous hydrogenolysis process was also evaluated. A two-stage cascade CSTR was determined appropriate for the multiphase reaction (see SI). Using the same 10% (w/w) catalyst loading, at 5 bar hydrogen pressure and 50 °C, and a flow rate of 4 mL/min ethyl acetate solution of **2** to give a Tres of 8 min, the steady-state conversion of starting material was >95% with reactions carried out for 1 h (7 reaction volumes). The isolated anisole yield was 70%, and remaining mass was identified as cresol 15%, along with 15% unidentified impurities.

Using the CSTR, the reaction reaches steady state after 20 min, and the catalyst appears not to decompose over 1 h operation, as in Figure 3.

The productivity was 45 g/L·h, with catalyst TOF 100 h^{-1}, and represents a 10-fold improvement over the batch method. Further development is likely to improve this. At twice the flow rate, the conversion dropped to 60%, while reuse of the catalyst gave 20% less anisole.

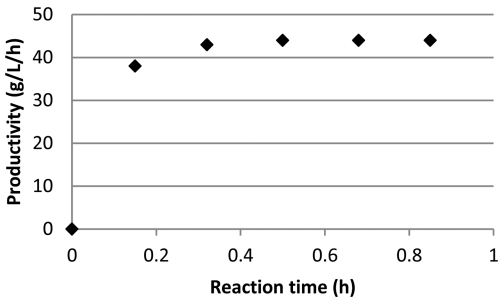


Figure 3. Productivity of anisole by Pd/C catalyzed hydrogenolysis of **2** at T_{res} = 8 min in CSTR.

CONCLUSIONS

A mild and selective continuous flow process has been developed, in which a variety of lignin-related phenols have been activated with cyanuric chloride and catalytically hydrodeoxygenated at mild temperatures and pressures by Pd/C and H_2. Further work will look at telescoping the two processes and using mixtures of phenols typical of lignin digests. Guaiacol has been converted to anisole with 81% yield over two steps using one-third of a mole equivalent of cyanuric chloride. The atom efficiency of the overall process is 48%, and the process mass intensity is 81, 96% of which is due to the solvents water, acetone, and ethyl acetate. A process for the continuous production of anisole has been developed giving 45 g/L·h over an hour, but clearly further improvements would need to be made before being commercially viable, including extended run times and a more thorough evaluation of the catalyst deactivation. Anisole is being increasingly used as a green solvent and reactant in the Pharma, Fine Chemical, Agrochemical, and Perfumery industries. Assuming guaiacol from lignin could be produced at £1/kg and a more efficient use was made of the Pd/C catalyst, the hydrodeoxygenation process described herein has the potential to compete with the petrochemical produced price of anisole.[20]

EXPERIMENTAL SECTION

Analytical Methods for the Determination of Chemical Purity by GC. Analyses were performed on an Agilent HP6890 chromatograph, using a capillary column HP-5 (5% phenyl methyl siloxane) HP 19091J-413; dimensions: 30 m × 320 μm × 0.25 μm; pressure: 4.3 psi; nominal initial flow: 1.6 mL/min; average velocity: 33 cm/s; equilibration time: 3; injection volume: 1 μL; oven: initial temperature: 60 °C; ramp: 20 °C/min to 200 °C; hold for 3 min; total run time = 16 min; inlet:mode: split ratio 10.7:1; temperature: 250 °C; split flow: 17.5 mL/min; total flow: 28.3 mL/min; gas saver: 20 mL/min;

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detector: temp: 250 °C; mode: constant flow; H_2 flow: 30 mL/min; air flow: 300.0 mL/min; makeup flow: 10 mL/min (N_2). Quantitative product analysis was calculated using the following method: a 0.10 mL solution of biphenyl (10 mg/L) containing a standard of the specific compound of interest (0.05 mL) in MeOH (1.00 mL). The retention times of commercial standards and pure products: (min) anisole, 2.00; benzene, 0.63; phenol, 3.28; cresol, 4.80; toluene, 1.13; 3-methylanisole, 5.80; 3-methoxybenzyl alcohol, 8.96; 3-methoxybenzaldehyde, 8.09; 2,4,6-*tris*(2-methoxyphenoxy)-1,3,5-triazine, 19.86.

General Information. All reagents and solvents were obtained from commercial suppliers and used as supplied unless stated otherwise. All yields refer to chromatographically and spectroscopically pure products unless stated otherwise. All NMR spectra were recorded on Bruker DPX-300 and DRX-500 spectrometers in the solvents specified. Infrared spectra were recorded neat on NaCl plates or as a solid on a diamond transmission accessory using a PerkinElmer FT-IR spectrometer; details are reported as ν_{max} in cm^{-1}. Mass spectra were carried out using a Micromass LCT (ES mode), Bruker Daltonic (ES mode), and Waters GCT Premier (EI and FI mode) apparatus and are reported as values in atomic mass units followed by the peak intensity relative to the base peak (100%). Elemental analysis was done using a Carlo Erba 1108 elemental analyzer apparatus. Crystal and molecular structures were determined using single crystal X-ray diffraction using Nonius KappaCCD and Bruker-Nonius FR591/X8Apex apparatus. Melting points were measured using a Griffin melting point apparatus and are uncorrected. Sulfonylated phenols used were synthesized and hydrogenolyzed using standard procedures; see SI. Tetrazoylguaicol was synthesized using the method of Alves et al.;[11] see SI.

General Method for the Synthesis of 1,3,5-Triaryloxy-2,4,6-triazines 1−10. A solution of cyanuric chloride (1 equiv) in acetone (300 mL) was added dropwise to a solution of the phenol (3 equiv) in water (300 mL) with NaOH (3 equiv) and the resulting solution stirred at room temperature for 3 h. The reaction mixture was filtered; the resulting solid was washed with water (2 × 100 mL) and crystallized.

*1,3,5-Triphenoxy-2,4,6-triazine (**1**).* **1** was recrystallized from MeOH to give a white solid (2.26 g, 6.32 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (ddd, J = 8.3, 7.4, 0.9 Hz, 9H, C3H/C4H/C5H), 7.16−7.10 (m, 6H, C2H/C6H). Lit ^{1}H NMR: δ = 7.25−6.60 (m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.68, 151.61, 129.44, 126.03, 121.39. HRMS (ES+ mode): m/z = 380.1020 [100%, MNa^+]; calculated for $C_{21}H_{15}N_3O_3$ requires [MNa^+]: m/z = 380.1006. Mpt. (MeOH) 230−232 °C; Lit.[21] Mpt. ($CHCl_3$/hexane) 230−231 °C.

*1,3,5-Tri(2-methoxyphenoxy)-2,4,6-triazine (**2**).* **2** was recrystallized from MeOH to give a white crystalline product (19.68 g, 44.03 mmol, 78%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.22 (ddd, J = 8.2, 7.4, 1.6 Hz, 3H, C5), 7.13 (ddd, J = 30.5, 8.1, 1.5 Hz, 6H, C4/C6), 6.93 (td, J = 7.7, 1.4 Hz, 3H, C3), 3.85 (s, 9H, OCH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.62, 151.16, 140.86, 126.80, 122.35, 120.60, 112.66, 55.79. HRMS (ES+ mode): m/z = 448.1509 [100%, MH^+]; calculated for $C_{24}H_{22}N_3O_6$ requires [MH^+]: m/z = 448.1506. IR υ_{max}/ cm^{-1} (film): 3017, 2836, 2097, 1695, 1596, 1476, 1253, 1202, 1166, 743. Analysis calculated (%) for $C_{24}H_{21}N_3O_6$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.15; H, 4.75; N, 9.25. Mpt. (MeOH) 139−141 °C; Lit.[22] Mpt. 145 °C.

*1,3,5-Tri(3-methoxyphenoxy)-2,4,6-triazine (**3**).* **3** was recrystallized from MeOH to give the product as a white solid (2.34 g, 5.24 mmol, 92%). ^{1}H NMR (501 MHz, $CDCl_3$) δ = 7.24 (s, 3H, C5H), 6.75 (dddd, J = 16.1, 8.1, 2.4, 0.8 Hz, 6H, C5H/C6H), 6.69 (t, J = 2.3 Hz, 3H, C2H), 3.76 (s, 9H, OCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.63, 160.49, 152.45, 129.80, 113.59, 111.88, 107.52, 55.41. LC-MS: m/z = 448.20 [100%, MH^+]; calculated for $C_{24}H_{21}N_3O_6$ requires [MH^+]: m/z = 448.15. IR υ_{max}/ cm^{-1} (film): 3011, 2840, 1576, 1269, 1146, 1040, 776. Mpt. 145−147 °C.

*1,3,5-Tri(4-methoxyphenoxy)-2,4,6-triazine (**4**).* **4** was recrystallized from MeOH to give the title product as a white solid (3.08 g, 6.97 mmol, 85%). ^{1}H NMR as described in the literature.[23] ^{13}C NMR (125 MHz, $CDCl_3$): 190.9, 173.6, 156.0, 134.8, 131.7, 122.6. HRMS (ES+ mode): m/z = 464.0870 [100%, MNa^+]; calculated for $C_{24}H_{15}N_3O_6$ requires [MNa^+]: m/z = 464.0853. Mpt. (MeOH) 168−170 °C; Lit.[24] Mpt. (EtOAc) 174−176 °C.

*1,3,5-Tri(4-formylphenoxy)-2,4,6-triazine (**5**).* **5** was filtered to give the product as a yellow solid (2.84 g, 6.35 mmol, 92%). ^{1}H NMR and Mpt. are as described in the literature.[25]

*1,3,5-Tri(2-methoxy-4-formylphenoxy)-2,4,6-triazine (**6**).* **6** was recrystallized from MeOH to give the title product as a white solid (2.16 g, 4.07 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.01 (s, 1H, CHO), 7.50 (d, J = 1.8 Hz, 1H, C5H), 7.49 (d, J = 1.8 Hz, 1H, C3H), 7.30 (d, J = 8.4 Hz, 1H, C6H), 3.86 (3H, s, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.79, 173.70, 151.70, 145.04, 135.73, 124.72, 122.71, 111.48, 56.26. HRMS (ES+ mode): m/z = 554.1176 [100%, MNa^+]; calculated for $C_{27}H_{21}N_3O_9$ requires [MNa^+]: m/z = 554.1170. IR υ_{max}/ cm^{-1} (film): 3012, 2835, 2563, 2097, 1694, 1593, 1466, 1263, 1202, 1174, 812, 732. Mpt. (MeOH) 238−240 °C.

*1,3,5-Tri(4-methoxycarbonylphenoxy)-2,4,6-triazine (**7**).* **7** was recrystallized from CH_2Cl_2 to give the title product as white solid (1.54 g, 2.90 mmol, 66%). ^{1}H NMR (501 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.7 Hz, 6H, C3H/C5H), 7.19 (d, J = 8.8, 6H, C2H/C6H), 3.93 (3H, s, $COOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.10, 166.80, 159.74, 131.92, 122.87, 115.89, 51.89. HRMS (ES+ mode): m/z = 554.1176 [100%, MNa^+]; calculated for $C_{27}H_{21}N_3O_9$ requires [MNa^+]: m/z = 554.1170. IR υ_{max}/ cm^{-1} (film): 2986, 1726, 1538, 1357, 1286, 1117, 739. Mpt. 148−151 °C.

*1,3,5-Tri(2-methoxy-4-methoxycarbonylphenoxy)-2,4,6-triazine (**8**).* **8** was recrystallized from CH_2Cl_2 to give the title product as a white solid (0.19 g, 0.30 mmol, 33%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (dd, J = 8.3, 1.9 Hz, 3H, C5H), 7.62 (d, J = 1.9 Hz, 3H, C3H), 7.16 (d, J = 8.3 Hz, 3H, C6H), 3.93 (s, 9H, OCH_3), 3.83 (s, 9H, $COOCH_3$). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.71, 164.10, 150.84, 142.00, 129.16, 124.62, 117.64, 112.29, 56.19, 52.07. LC-MS: m/z = 622.22 [100%, MH^+]; calculated for $C_{30}H_{27}N_3O_{12}$ requires [MH^+]: m/z = 622.16. IR υ_{max}/ cm^{-1} (film): 2975, 1718, 1538, 1357, 1291, 1174, 739. Mpt. 251−253 °C.

*1,3,5-Tri(4-benzoyloxy)-2,4,6-triazine (**9**).* After filtration and vacuum drying, the product was obtained as a white solid (1.54 g, 3.15 mmol, 76%). ^{1}H NMR was as described in the literature.[26] ^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.70, 166.41, 154.53, 130.90, 128.59, 121.61. HRMS (ES+ mode): m/z = 490.0883 [100%, MH^+]; calculated for $C_{24}H_{15}N_3O_9$ requires [MH^+]: m/z = 490.0881. Mpt. 329−331 °C; lit.[26] mpt. > 300 °C.

*1,3,5-Tri(2-methoxy-4-carboxy)-2,4,6-triazine (**10**).* After filtration and vacuum drying, the product was obtained as a yellow solid (1.40 g, 2.41 mmol, 71% yield). ^{1}H NMR (501 MHz, DMSO-d_6): δ = 13.04 (brs, 3H, COOH), 7.61−7.50 (m,

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6H, C5H/C6H), 7.31 (d, J = 8.3 Hz, 3H, C3H), 3.78 (s, 9H, OCH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 172.74, 166.40, 150.45, 143.24, 129.88, 122.48, 122.11, 113.40, 55.99. HRMS (ES+ mode): m/z = 580.1209 [100%, MH^+]; calculated for $C_{27}H_{21}N_3O_{12}$ requires [MH^+]: m/z = 579.1198. IR υ_{max}/ cm^{-1} (film): 3071, 2957, 1618, 1497, 1367, 1292, 1179, 805. Mpt. 313−315 °C

Synthesis of 1,3,5-Tri(2-methoxyphenoxy)-2,4,6-triazine (2) in Continuous Flow. A solution of cyanuric chloride (0.083 g, 0.45 mmol) in acetone (25 mL) was added to one syringe. A solution of guaiacol (0.25 g, 2 mmol) in water (25 mL) and NaOH (0.25 g, 6.25 mmol) was added to the second syringe. The solutions were pumped through a four-stage cascade CSTR (see SI for picture), at 0.26 mL/min, giving a residence time of 30 min. The reaction was run for 2.5 h, and 5 RVs were collected. Each RV was then filtered and the solid washed with water (2 × 15 mL), yielding off-white crystals of **2** (0.28 g, 16%). Each reactor volume was analyzed by NMR and the spectra consistent with those reported for **2** above.

General Procedure for the Hydrogenolysis of Triaryloxytriazines in Batch. To a solution of the triaryloxytriazine (1.00 equiv) in ethyl acetate (60 mL) was added 10% Pd/C (10 wt % age of the substrate) at room temperature. The mixture was degassed of oxygen three times by vacuum/nitrogen cycles. The flask was degassed of nitrogen three times by vacuum/hydrogen cycles and left under a reservoir of hydrogen at atmospheric pressure from a balloon. Separate reactions were stirred for 6−21 h at 20 or 40 °C. When the hydrogenation was complete, the catalyst was removed by filtering through a plug of Celite. The filtrate was washed with water (20 mL), and the organic layer was separated and dried with $MgSO_4$ and concentrated in vacuo.

General Procedure for the Hydrogenolysis of Triaryloxytriazines in Continuous Flow. A two-stage cascade CSTR 0.6 L Hastelloy automated Parr hydrogenator was employed; see SI for picture. A 12.5 g/L solution of the triazine in EtOAc was pumped into the first reactor containing the resident volume of ethyl acetate, 10% (w/w) of catalyst mechanically stirred under a hydrogen atmosphere, controlled at a temperature of 40 °C. The hydrogen pressure, flow rate, and residence volume were varied to optimize the reaction conditions; see SI Table 2 for details. The residence volume could be changed by adjusting the length of the dip tube in both reactors; the product was collected continuously in a column connected in series. After venting the hydrogen the products were obtained by screening the catalyst using solvent-wet Celite on a sintered filter, washed with additional solvent, and the deoxygenated aromatic product was analyzed directly in solution by quantitative GC against authentic standards. In some experiments the solvent was carefully removed to give the product oils, and the structures were confirmed by ^1H NMR and found to be consistent with published data.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00314.

Analytical details; experimental information on other compounds discussed in the paper; details of continuous flow experiments using CSTRs; information about cyanuric acid decomposition and catalyst deactivation; raw material cost information; crystal structure X-ray data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.blacker@leeds.ac.uk.

Notes

The authors declare no competing financial interest.

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